

19 592 MELOXICAM

=> d hist

(FILE 'HOME' ENTERED AT 12:04:59 ON 05 NOV.2001)

FILE 'REGISTRY' ENTERED AT 12:05:32 ON 05 NOV 2001

L1 0 S CELICOXIB

L2 1 S CELEBREX

FILE 'CAPLUS, MEDLINE' ENTERED AT 12:07:01 ON 05 NOV 2001

L3 504 S L2

L4 135766 S HEPATITIS

L5 7 S L4 AND L3

L6 7 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)

L7 5527 S COX-2

L8 5823 S CYCLOOXYGENASE-2 OR CYCLOOXYGENASE (W) (2 OR II)

L9 7537 S L8 OR L7

L10 24 S L9 AND L4

L11 20 DUPLICATE REMOVE L10 (4 DUPLICATES REMOVED)

L12 340843 S ANTI-INFLAMM? OR INFLAMMAT?

L13 3966 S L12 AND L9

L14 911 S L13 AND INFLAMMAT?/TI

L15 110 S L14 AND COX-2/TI

L16 0 S L15 AND LIVER

L17 29 S L15 AND PY<=1997

L18 21 DUPLICATE REMOVE L17 (8 DUPLICATES REMOVED)

L19 592 S MELOXICAM

=> s l19 and l4

L20 2 L19 AND L4

=> s anti-inflamm? or inflammat?

L12 340843 ANTI-INFLAMM? OR INFLAMMAT?

=> d hist

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L14 911 L13 AND INFLAMMAT?/TI

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=> s l14 and cox-2/ti

L15 110 L14 AND COX-2/TI

=> s l15 and liver

L16 0 L15 AND LIVER

=> s l15 and py<=1997

L17 29 L15 AND PY<=1997

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**Today's Date:** 11/5/2001

<u>DB Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
JPAB,EPAB,DWPI	l22 and l21	17	<u>L23</u>
JPAB,EPAB,DWPI	hepatitis	9504	<u>L22</u>
JPAB,EPAB,DWPI	l17 or l18 or l19 or l20	506	<u>L21</u>
JPAB,EPAB,DWPI	cyclooxygenase adj II	26	<u>L20</u>
JPAB,EPAB,DWPI	cyclooxygenase adj 2	372	<u>L19</u>
JPAB,EPAB,DWPI	cyclooxygenase-2	345	<u>L18</u>
JPAB,EPAB,DWPI	cox-2	298	<u>L17</u>
USPT	17 and l13	36	<u>L16</u>
USPT	17 and l2	21	<u>L15</u>
USPT	l13 and l2	0	<u>L14</u>
USPT	hepatitis	12548	<u>L13</u>
USPT	18 and l2	3	<u>L12</u>
USPT	l8.clm. and l7.clm.	2	<u>L11</u>
USPT	18 and l7.clm.	13	<u>L10</u>
USPT	18 and l7	88	<u>L9</u>
USPT	liver or hepatitis or cirrhosis or steatohepatitis	43017	<u>L8</u>
USPT	l3 or l4 or l5	301	<u>L7</u>
USPT	s l3 or l4 or l5	301	<u>L6</u>
USPT	cyclooxygenase adj II	51	<u>L5</u>
USPT	cyclooxygenase adj 2	254	<u>L4</u>
USPT	cyclooxygenase-2	229	<u>L3</u>
USPT	5466823	30	<u>L2</u>
USPT	5466823.pn.	1	<u>L1</u>

L18 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4

ACCESSION NUMBER: 1996:356036 CAPLUS

DOCUMENT NUMBER: 125:31441

TITLE: Selective inhibition of cyclooxygenase (COX)-2 reverses inflammation and expression of COX-2 and cyclooxygenase (COX)-2 in rat adjuvant arthritis

AUTHOR(S): Anderson, Gary D.; Hauser, Scott D.; McGarity, Kelly L.; Bremer, Margaret E.; Isakson, Peter C.; Gregory, Susan A.

CORPORATE SOURCE: Dep. of Inflammatory Diseases Res. and Cell and Molecular Biology, G.D. Searle & Company, St. Louis, MO, 63198, USA

SOURCE: J. Clin. Invest. (1996), 97(11), 2672-2679  
CODEN: JCINAO; ISSN: 0021-9738

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Prostaglandins formed by the cyclooxygenase (COX) enzymes are important mediators of inflammation in arthritis. The contribution of the inducible COX-2 enzyme to inflammation in rat adjuvant arthritis was evaluated by characterization of COX-2 expression in normal and arthritic paws and by pharmacol. inhibition of COX-2 activity. The injection of adjuvant induced a marked edema of the hind footpads with coincident

local

prodn. of PGE2. PG prodn. was assocd. with upregulation of COX-2 mRNA and protein in the affected paws. In contrast, the level of COX-1 mRNA was unaffected by adjuvant injection. TNF-.alpha. and IL-6 mRNAs were also increased in the inflamed paws as was IL-6 protein in the serum. Therapeutic administration of a selective COX-2 inhibitor, SC-58125, rapidly reversed paw edema and reduced the level of PGE2 in paw tissue to baseline. Interestingly, treatment with the COX-2 inhibitor also reduced the expression of COX-2 mRNA and protein in the paw. Serum IL-6 paw IL-6 mRNA levels were also reduced to near normal levels by SC-58125. Furthermore, inhibition of COX-2 resulted in a redn. of the inflammatory cell infiltrate and decreased inflammation of the synovium. Notably, the antiinflammatory effects of SC-58125 were indistinguishable from the effects obsd. for indomethacin. These results suggest that COX-2 plays a prominent role in the inflammation assocd. with adjuvant arthritis and that COX-2 derived PGs upregulate COX-2 and IL-6 expression at inflammatory sites.

18 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 1996:512202 CAPLUS  
DOCUMENT NUMBER: 125:184577  
TITLE: **COX-2** inhibitors. Potential for  
reducing NSAID side-effects in treating  
**inflammatory** diseases  
AUTHOR(S): Carty, T. J.; Marfat, A.  
CORPORATE SOURCE: Central Research Division, Pfizer, Inc., Groton, CT,  
06340, USA  
SOURCE: Emerging Drugs (1996), 1, 391-411  
CODEN: EMDRFV; ISSN: 1361-9195  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review with 82 refs. Downregulation of prostaglandin (PG) formation is essential for the removal of the painful symptoms of **inflammation**, ranging from sports injuries to rheumatoid arthritis. Nonsteroidal **anti-inflammatory** drugs (NSAIDs, e.g., indomethacin, piroxicam), are well recognized to be clin. efficacious by controlling PG formation through the inhibition of cyclooxygenase (COX), a key enzyme in the PG synthetic cascade. The use of NSAIDs, however, can be limited by their gastrointestinal (GI) and renal side-effects, esp. in the elderly. Recent research has shown that cellular synthesis of PG is derived from two different forms of COX, a constitutive (naturally present) isoform (COX-1) used for the maintenance of organ function (e.g., the GI tract), and an inducible isoform (**COX-2**) employed for the prodn. of large amts. of PG synthesized during **inflammation**. Since most NSAIDs inhibit both isoforms, this finding has provided a unique opportunity to discover a pharmacol. agent with specificity for inhibiting **COX-2**, with little or no effect on COX-1. While retaining the efficacy of conventional NSAIDs, **COX-2**-selective NSAIDs are expected to display no deleterious effects on the GI tract, thus providing significantly improved toleration. Although it is not clear what their effect will be on the kidney, **COX-2**-selective agents should offer a pharmacol. profile that predominantly targets PGs produced at the **inflammatory** site. Should ongoing clin. trials prove the **COX-2** concept, this class of compds. could provide a new and exciting generation of **anti-inflammatory** drugs, which, we would like to propose, could be called **COX-2**-SAIDs, for **COX-2**-selective **anti-inflammatory** drugs.

L11 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:33593 CAPLUS

DOCUMENT NUMBER: 128:162452

TITLE: Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition?

AUTHOR(S): Davies, Neal M.

CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology and Therapeutics, Intestinal Disease Research Unit, University of Calgary, Calgary, AB, Can.

SOURCE: Clin. Pharmacokinet. (1997), 33(6), 403-416

CODEN: CPKNDH; ISSN: 0312-5963

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 45 refs. Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) of the 2,6-disubstituted naphthyl-alkanone class.

Nabumetone

is metabolized to an active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA) which is a relatively selective cyclo-oxygenase-2 inhibitor that has anti-inflammatory and analgesic properties. Nabumetone and its metabolites bind extensively to plasma albumin. Nabumetone is eliminated following biotransformation to 6-MNA, which does not undergo **enterohepatic** circulation and the resp. glucoroconjugated metabolites are excreted in urine. Substantial concns. of 6-MNA are attained in synovial fluid, which is the proposed site of action in chronic inflammatory arthropathies. A smaller area under the plasma concn.-time curve (AUC) is evident at steady state as compared with a single dose; this is possibly due to an increase in the vol. of distribution and satn. of protein binding. Relationships between 6-MNA concns. and the therapeutic and toxicol. effects have yet to be

elucidated

for this NSAID. Renal failure significantly reduces 6-MNA elimination but

steady-state concns. of 6-MNA are not increased, possibly because of nonlinear protein binding. Elderly patients with osteoarthritis demonstrate decreased elimination and increased plasma concns. of nabumetone as compared with young healthy volunteers. Rheumatic disease activity also influences 6-MNA plasma concns., as patients with more active disease and lower serum albumin concns. demonstrate a lower area under the plasma concn. vs. time curve. A reduced bioavailability of 6-MNA in patients with severe **hepatic** impairment is also evident. Dosage adjustment may be required in the elderly, patients with active rheumatic disease and those with **hepatic** impairment, but not in patients with mild-to-moderate renal failure.

L11 ANSWER 20 OF 38 MEDLINE DUPLICATE 10  
 ACCESSION NUMBER: 97362852 MEDLINE  
 DOCUMENT NUMBER: 97362852 PubMed ID: 9219316  
 TITLE: Meloxicam: selective COX-2 inhibition  
 in clinical practice.  
 AUTHOR: Furst D E  
 CORPORATE SOURCE: Arthritis Clinical Research Unit, Virginia Mason Research  
 Center, Seattle, WA 98101, USA.  
 SOURCE: SEMINARS IN ARTHRITIS AND RHEUMATISM, (1997 Jun)  
 26 (6 Suppl 1) 21-7. Ref: 24  
 Journal code: UMV; 1306053. ISSN: 0049-0172.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199708  
 ENTRY DATE: Entered STN: 19970902  
 Last Updated on STN: 19970902  
 Entered Medline: 19970819

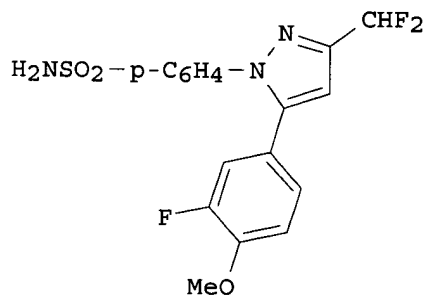
AB Nonsteroidal antiinflammatory drugs (NSAIDs) exert their actions by  
 inhibiting cyclooxygenase (COX). It has recently been postulated that  
 NSAIDs' antiinflammatory efficacy arises from inhibition of the  
 COX-2 isoform of cyclooxygenase, whereas inhibition of  
 the COX-1 isoform produces the troublesome and sometimes serious gastric  
 and renal side effects of NSAIDs. A relatively selective COX-  
 2 inhibitor, such as meloxicam, may combine antiinflammatory  
 efficacy with improved tolerability. In volunteers, indomethacin 75 mg,  
 but not meloxicam 7.5 mg, inhibited renal prostaglandin E2 excretion and  
 platelet aggregation (COX-1 mediated effects). Double-blind, randomized  
 trials in osteoarthritis and rheumatoid arthritis patients have shown  
 equivalent antiinflammatory efficacy among meloxicam 7.5 mg or 15 mg and  
 diclofenac 100 mg, naproxen 750 mg, and piroxicam 20 mg. In a  
 double-blind, placebo-controlled trial, meloxicam (7.5 or 15 mg) caused  
 less endoscopically detected gastrointestinal (GI) damage (Lanza scale)  
 than piroxicam 20 mg. The MELISSA study, a double-blind, randomized,  
 28-day trial in over 9,000 patients showed that meloxicam 7.5 mg caused  
 statistically less total GI toxicity, dyspepsia, abdominal pain, nausea  
 and vomiting, and diarrhea than diclofenac 100 mg, despite equivalent  
 reductions in pain on movement for each treatment. A global safety  
 analysis of clinical trials, representing over 5,600 patients and  
 comprising 170 and 1,100 patient-years of exposure for meloxicam 7.5 mg  
 and 15 mg, respectively, showed that meloxicam caused less GI toxicity  
 and  
 fewer peptic ulcers and GI bleeds than naproxen, diclofenac, or  
 piroxicam.

The renal safety profile and incidence of liver function  
 abnormalities with meloxicam is equivalent to other NSAIDs available for  
 clinical use. In conclusion, relatively selective COX-2  
 inhibition exemplified by meloxicam may offer effective symptom relief  
 with an improved GI tolerability profile.



ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 1997:562995 CAPLUS  
 DOCUMENT NUMBER: 127:225303  
 TITLE: Immunosuppressive combinations containing a  
**cyclooxygenase-2** inhibitor and a  
 leukotriene A4 hydrolase inhibitor  
 INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary  
 PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson,  
 Peter C.; Anderson, Gary  
 SOURCE: PCT Int. Appl., 77 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729774	A1	19970821	WO 1997-US1421	19970211 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246336	AA	19970821	CA 1997-2246336	19970211 <--
AU 9719525	A1	19970902	AU 1997-19525	19970211 <--
EP 880363	A1	19981202	EP 1997-907545	19970211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001506574	T2	20010522	JP 1997-529358	19970211
PRIORITY APPLN. INFO.:			US 1996-600655	A1 19960213
			WO 1997-US1421	W 19970211
OTHER SOURCE(S):		MARPAT 127:225303		
GI				



AB Immunosuppressant compns. contg. a combination of a **cyclooxygenase** -2 inhibitor (which inhibits conversion of arachidonic acid to prostaglandins) and a LTA4 hydrolase inhibitor are useful in reducing recipient rejection of **transplanted** organs and for treatment of autoimmune diseases. Thus, F<sub>2</sub>CHCO<sub>2</sub>Et reacted with 3-fluoro-4-

methoxyacetophenone to form 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione, which was condensed with 4-sulfonamidophenylhydrazine-HCl to produce the **cyclooxygenase-2** inhibitor I. A formulation was prepd. contg. 350 mg I and 700 mg 3-[N-methyl-N-[3-[(4-phenylmethyl)phenoxy]propyl]aminol]propanoic acid (LTA4 hydrolase inhibitor).

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:562996 CAPLUS

DOCUMENT NUMBER: 127:239123

TITLE: Combinations having immunosuppressive effects,  
containing **cyclooxygenase-2**

-inhibitors and 5-lipoxygenase inhibitors

INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary

PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson,

Peter C.; Anderson, Gary

SOURCE: PCT Int. Appl., 68 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729776	A1	19970821	WO 1997-US1558	19970212 <--
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
CA 2246265	AA	19970821	CA 1997-2246265	19970212 <--
AU 9718505	A1	19970902	AU 1997-18505	19970212 <--
EP 888127	A1	19990107	EP 1997-904133	19970212
EP 888127	B1	20011212		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI			
JP 2000504723	T2	20000418	JP 1997-529363	19970212
PRIORITY APPLN. INFO.:			US 1996-600622	A1 19960213
			WO 1997-US1558	W 19970212

OTHER SOURCE(S): MARPAT 127:239123

AB Treatment with a **cyclooxygenase-2** inhibitor and a 5-lipoxygenase inhibitor is described as being useful in reducing recipient rejection of **transplanted** organs and for treatment of autoimmune diseases. 4-[5-(3-Fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and

N'-[3-[5-(4-fluorophenoxy)-2-furyl]-1-methyl-2-propynyl]-N'-hydroxyurea were prepd. and a combination of these

2 compds. showed a delay in rejection time of skin grafts while treatment alone of each of these compds. resulted in no prolongation of graft survival.